UK Patent Application (19) GB (11) 2 153 676 A

(43) Application published 29 Aug 1968

(21)	Application No 8503032	(51) INT CL ⁴ A61K 9/00 31/74 47/00	
(22)	Date of filing 6 Feb 1965	(52) Domestic classification A68 832 833 835 N	
(30)	Priority data	740 COL 101 101	
	(31) 8403361 (32) 8 Feb 1984 (33) GB	(58) Documents cited GB 1573459 EP A 0068448	EP A 0053590
	Applicent Formitalis Carlo Erbs SpA (italy), Via Carlo Imboneti 24, 20159 Milan, italy	(58) Field of search A5B	
(72)	Inventor Febio Caril		•
(74)	Agent and/or Address for Service J. A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5EU		

(54) Pharmaceutical composition

⁽⁵⁷⁾ A water-swellable, water-insoluble polymer is loaded with a biologically active substance or substance which is converted thereinto in vivo, for example a drug or pro-drug, by preparing a mixture of a said substance with a thermally stable water-swallable, water-insoluble polymer in a weight ratio of the said substance: polymer of from 1:0.1 to 1:100 and heating said mixture up to the malting temperature of the said substance. The thus-loaded polymer is useful as a pharmaceutical composition.

GB 2 153 678 A

SPECIFICATION

Pharmacautical composition

g. This invention relates to the preparation of formulations comprising a biologically active substance or substance which is converted thereinto in vivo.

5

The wettability and dissolution properties of a biologically active substance or substance which is converted thereinto in vivo such as a drug or pro-drug greatly influence its bioevallability. In many cases very active drugs or pro-drugs, for example, present a poor abcorption profile due to their unfavourable 10 dissolution characteristics. Reduction of their particle size and addition of westing agents, widely applied to overcome these problems, very frequently prove to be not effective enough. Therefore much effort has been devoted to develop new formulations or new techniques to get better results. Considerable attention have recently gained two new research lines besed on the preparation of "solid dispersions" and of "inclusion compounds". In the former approach the drug or pro-drug is molecularly dispersed in the carrier, usually a 15 water-coluble polymer (S. Riegelman, W.L. Chlou 987,588 4/1978 Canada), while in the latter the drug or pro-drug forms molecular complexes with water-soluble cyclodextrins (J. Szejtli "Cyclodextrins and thair inclusion compounds". Akademie Viedo, Budepest 1882).

18

10

A remerkable enhancement of the discolution and bloavellability of poorly water-colubia aubstances can be also achieved by the procedure of the present invention in which a biologically active substance or 20 substance converted thereinto in vivo is loaded in/on swellable, water-insoluble polymers by heating up to the melting temperature of the substance mixtures of substances and said polymers. Specifically, if a drug or pro-drug has physico-chemical characteristics which are unfavourable (poor wettability, poor dissolution characteristics in aqueous media) to its in vivo absorption, heating a mixture of it and a swellable water-insoluble polymer improves these characteristics and consequently can bring about an enhanced 25 blosvailability.

25

20

This is due to one or both the following effects brought about by the heating process:

1. Increase of wettability of the drug or pro-drug as consequence of the very large dispersion of it in/on the network of the highly hydrophylic and swellable polymer.

30

2. Increase of solubility caused by a complete or partial transition of the original crystalline network of the 30 drug or pro-drug to a higher energy (lower melting point) structure and/or to a completely or partially amorphous form. In addition to the above specified advantages, the drug or pro-drug leaded on the aforementioned

35

polymers may also present other improved chemico-physical or technological properties. Accordingly, the present invention provides a process for loading a water-swellable water-insoluble 35 polymer with a biologically active substance or substance which is converted thereinto in vivo, which process comprises (I) preparing a mixture of a said substance with a water-swellable water-insoluble polymer which is stable under the heating to which the imbiture is subjected in step (ii) in a weight ratio of the said substance: polymer of from 1:0.1 to 1:100 and (III) heating said mixture up to the melting temperature of

The present invention also provides a water-swellable, water-insoluble polymer which has been loaded with a biologically active substance or substance which is converted thereinto in vivo in a weight ratio of the said substance: polymer of from 1:0.1 to 1:100 by the precess of the invention.

45

The biologically active substance or substance which is converted thereinto in vivo is preferably a drug or pro-drug. For convenience hereinefter drugs and pro-drugs will be referred to collectively as "drugs", with 05 reference to which the precent invention will be described by way of example below.

The basic adventages of the drug polymer systems obtained according to the present invention are:

1. Remarkable increase of the drug wereability due to the high hydrophilicity and swelling capacity in water of the hydrophilic, swellable, weter-insoluble polymers.

2. Rapid swelling and disintegration in water of the system and immediate disparsion of the drug. Some of 60 the hydrophilic, swellable, water-insoluble polymers which may be used in the present process are in fact already used and marketed so disintegrants for oral solid dosage forms.

60

3. Avoidance of the viscous layer around the drug which can be related with the use of water-soluble polymers and which can hinder the drug diffusion and slow down the dissolution process.

in addition, loading of drugs in/on available water-insoluble polymers by the coheating technique 65 presents advantages over the loading method based on awalling of the polymer in an organic solvent containing the drug (B.C. Lippoid et al., D.O.S., 2,634,004). The basic adventages of the coheating technique over the owelling method are:

53

1. The evoldence of ell the problems of texicity and inflammability related to the use of solvents.

2. The possibility of loading larger quantities of drug on/in the awellable polymer; in feat the maximum 80 amount of drug which can be loaded by the solvent swelling method is limited both by the swelling volume and the colubility of the drug in that solvens.

ഒ

3. At low drug/ewellable polymer ratio, better dissolution and consequently also better bloavallability can be achieved by the heated mixture compared to the solvent loaded mixture, as the heating technique can lead about higher dagree of amorphization.

65

This invention is concerned with the heating up to the mailting temperature of the drug of a mixture of an

2

5

10

18

20

25

30

35

Z٩

AUS.

80

55

60

85

active drug and any water-insoluble, hydrophylic, swellable polymer (or combination of two or more thereof). Non-limiting examples of such polymers ere:

a) crosslinked FVP (National Formulary XV, Supplement 3, page. 368), hereofter shortened in crosslinked

b) crosslinteed scallum carbonymethylcollulose (National Formulary XV, Supplement 3, page 385); 5 c) crosslinked dextren etc.

The common characteristics of these polymers are:

1. High swalling ability in water (from 0.1 mi to 100 ml of water volume uptake par gram of drug polymer). This characteristic brings about a high swelling and an effective disintegration (in water or in biological 10 fluids) of the systems with a powerful dispersion of its constituents and an immediate release of the drug molecules.

2. Fast rate of water swalling (e.g. crosslinked PVP achieves maximum swelling in less than five minutes). This property allows that the aforementioned effects of swalling, disintegration, dispersion and dissolution of the drug molecules are accomplished in a very phort period of time.

3. Water insolubility. This property rules out possible negative effects able to slow down the drug dissolution process, e.g. by building up a viscous layer around the drug, and brings about the formation of a finely dispersed suppension which sesures a rapid gestric emptying to the absorption site.

4. No degradation or melting up to the melting temperature of the drug. In other words, the polymer must be thermally stable under the heading to which it is subjected. This means, for example, that crosslinked PVP, 20 which, in a controlled atmosphere, dose not present any detectable degradation up to 300°C, can be used for the treatment of drugs with high melting temperatures; on the contrary, crosslinked dextron (caremalization temperature 120°C) can be used only with drugs with melting temperatures below 120°C; etc. The basic procedure of the heating technique of a mixture of an active drug and any (or combinations thereof) water-insoluble, swallable, hydrophylic polymer to which this invention relates, can be detailed as

A dry mixture of the drug and any of the swellable insoluble polymers aforementioned (chosen among those with good thermal stability at the melting point of the drug) is placed in a container incide o thermoregulated high vacuum oven; after evacuation a nitrogen flow is established over the drug-polymer mixture and temperature relead to a value higher than the melting point of the drug. Alternatively the 30 mixture of the drug and the polymer is pieced in the glass flask of a rotating evaporator; after evacuation, o flow of nitrogen is established over the drug-polymer mixture and the glass flask placed in an oil both at a temperature higher than the maiting point of the drug. Any other heating apparatus (hot plats, muffle, tube oven etc.) can be usefully applied, as long as the temperature can be carefully checked and held constant. In any case the temperature must be raised to a value sufficient to ensure the molting of the drug.

The drug-polymer mixture is hested so long as the desired degree of smorphization of the drug is achieved, which can be checked by Differential Scanning Calorimetry. In fact the absence in the thermogram of the peak releave to the solid/liquid transition of the crystelline drug means the product is completely amorphous (enthalpy of melting equal to zero). Obviously the heating process can be also stopped any time a dagree (0-100%) of amorphization (measured by the reduction of the melting enthalpy) sufficient to 40 sensibly incresso the dissolution rate is achieved. Alternatively, the heating process can be stopped any time the original crystalline form of the drug has been transformed into another, more energedic form (this transformation is indicated by the shifting of the original endothermic peak to lower temperatures), leading to higher dissolution rate and bioevallability.

Weight ratios of drug and the polymer in the mixture to be heated can vary from 1:0.1 to 1:100 w.w. drug: 45 polymer, proferably from 1:1 to 1:100 w.w. drug:polymer. For each drug: polymer weight ratio composition and each total amount of mbdure, the time of heating necessary to achieve the desired degree of amorphization must be checked; therefore for each drug-polymer system the most precitical combination of weight ratio and time of heating can be identified.

Examples of drug: polymer weight ratio compositions, of heating temperature and time will be given later. The resulting heated mixture of the active drug and the swellable insoluble polymer can then be forced through a sieve to aliminate possible aggregates and subsequently mixed in any mixing device to warrant further homogeneity. The resulting powdered heated system of the drug and the swellable polymer can be subsequently used to propere any desired design form (e.g., copsules, tablets etc.) with or without the addition of any of the common excipionts used in pharmaceutical formulations. Any active drug with poor 55 dissolution characteristics can be treated by the owellable polymer coheating technique described by this Invention. Non limiting examples of classes of drugs are: slightly colubia staroid hormones; non-craroidal hormones; antibiotics; antiminementary drugs; sedative drugs; etc. The amount of the polymer/drug system of the invention which is administered to a subject will depend upon a veriety of factors including the drug employed, the condition to be treated and the age and condition of the patient.

60 The following non-limiting examples illustrate methods of making the preparations of the present invention.

Example 1

0.15 gram of crystalline methylhydroxyprogeoterone ഓഫോ (MAP) and 0.75 gram of crosslinked PVP ware mixed with a autable mixing apparatus, subsequently placed in the glass flesk of a rotating evaporator and 65 heated in an oil both at 216°C for 45 minutes, under nitrogen flow. The resulting MAP / crosslinked PVP

JUL 29 '99 11:43 7034124866 PAGE. 04

SPECIFICATION

Phormozzadeci composition

5 This invention relates to the preparation of formulations comprising a biologically active substance or substance which is converted thereinto in vivo.

8

10

The wettability and dissolution properties of a biologically active aubstance or substance which is converted thereinto in vivo such so a drug or pro-drug greatly influence its bloavailability. In many cases very active drugs or pro-drugs, for example, present a poor absorption profile due to their unfavourable dissolution characteristics. Reduction of their particle size and addition of wetting agents, widely applied to overcome these problems, very frequently prove to be not effective enough. Therefore much effort has been devoted to develop new formulations or new techniques to get batter results. Considerable attention have recently gained two new research lines beand on the preparation of "solid dispersions" and of "inclusion compounds". In the former approach the drug or pro-drug is molecularly dispersed in the carrier, usually a water-soluble polymer (S. Riegelman, W.L. Chiou 987,588 4/1876 Canada), while in the latter the drug or pro-drug forms molecular complexes with water-soluble cyclodextrins (J. Szejtli "Cyclodextrins and their inclusion compounds", Atademia Viado, Budapest 1982).

15

A remarkable enhancement of the dissolution and bloavellability of poorly water-coluble substances can be also achieved by the procedure of the present Invention in which a biologically active substance or substance converted thereinto in vivo is loaded inton swellable, water-insoluble polymers by heating up to the metting temperature of the substance mixtures of substances and said polymers. Specifically, if a drug or pro-drug has physico-chemical characteristics which are unfavourable (poor westability, poor dissolution characteristics in aqueous media) to its in vivo absorption, heating a mixture of it and a swellable water-insoluble polymer improves these characteristics and consequently can bring about an enhanced bloaveilability.

23

This is due to one or both the following effects brought about by the heating process:

1. Increase of westability of the drug or pro-drug as consequence of the very large dispersion of it in/on the network of the highly hydrophylic and swellable polymer.

2. Increase of solubility caused by a complete or partial transition of the original crystalline network of the drug or pro-drug to a higher energy (lower melting point) structure and/or to a completely or partially amorphous form.

30

S

In addition to the above openified advantages, the drug or pro-drug loaded on the aforementioned polymers may also precent other improved chemico-physical or technological properties.

Accordingly, the present invention provides a process for loading a water-awallable water-insoluble polymer with a biologically active substance or substance which is converted thereinto in vivo, which process comprises (i) preparing a mixture of a said substance with a water-swallable water-insoluble polymer which is stable under the heating to which the mixture is subjected in step (ii) in a walght ratio of the said substance: polymer of from 1:0.1 to 1:100 and (iii) heating said mixture up to the melting temperature of the said substance.

ature of

The precant invention also provides a water-awellable, water-insoluble polymer which has been loaded with a biologically active substance or substance which is converted thereinto in a weight ratio of the said substance:polymer of from 1:0.1 to 1:100 by the process of the invention.

45

The biologically active substance or substance which is converted thereints in vivo is preferably a drug or pro-drug. For convenience hereinafter drugs and pro-drugs will be referred to collectively as "drugs", with reference to which the present invention will be described by way of example below.

The basic advantages of the drug polymer systems obtained according to the present invention are:

1. Remarkable increase of the drug wettebility due to the high hydrophilicity and swelling capacity in water of the hydrophilic, swellable, water-insoluble polymers.

2. Rapid awelling and disintegration in water of the system and immediate dispersion of the drug. Some of the hydrophilic, swellable, water-insoluble polymers which may be used in the present process are in fact already used and marketed as disintegrants for oral solid dosage forms.

50

3. Avoidance of the viscous layer around the drug which can be related with the use of water-coluble polymers and which can hinder the drug diffusion and slow down the dissolution process.

In addition, loading of drugo in/on swellable water-incoluble polymers by the cohesting technique precents advantages over the loading method based on swelling of the polymer in an organic solvent containing the drug (B.C. Lippoid et al., D.O.S., 2,834,004). The basic advantages of the cohesting technique over the swelling method ere:

55

හ

- 1. The evoidence of all the problems of toxicity and inflammability related to the use of solvents.
- 2. The possibility of loading larger quantities of drug on/in the swellable polymer; in fact the maximum amount of drug which can be loaded by the colvent swelling method is limited both by the swelling volume and the solubility of the drug in that solvent.

and the solubility of the drug in that solvent.

3. At low drug/swellable polymer ratio, before discolution and consequently also before bloavailability can be achieved by the heated mixture compared to the colvent loaded mixture, so the heating technique con

lead about higher degree of amorphization.

This invention is concerned with the heating up to the making temperature of the drug of a mixture of an

Б

10

15

20

26

30

335

40

48

50

55

മ്മ

85

active drug and any weter-inscluble, hydrophylic, swellable polymer (or combination of two or more thereof). Non-limiting examples of such polymers are:

a) crosslinked PVP (National Formulary XV, Supplement 3, page. 368), hereafter shortened in crosslinked PVP:

b) crosslinked codium carboxymethylesilulese (National Formulary XV, Supplement 3, page 385); c) crosslinked dextron etc.

The common characteristics of these polymers are:

1. High swalling ability in water (from 0.1 ml to 100 ml of water volume uptake per gram of drug polymer). This characteristic brings about a high swalling and an affective disintegration (in water or in biological 10 fluids) of the systems with a powerful dispersion of its constituents and an immediate release of the drug molecules.

2. Fast rate of water awalling (e.g. crosslinted PVP achieves maximum swelling in less than five minutes). This property allows that the aforementioned effects of swelling, disintegration, dispersion and dissolution of the drug molecules are accomplished in a very short period of time.

3. Water insolubility. This property rules out possible negative effects able to slow down the drug dissolution process, e.g. by building up a viscous layer around the drug, and brings about the formation of a finely dispersed suspension which assures a rapid gastric emptying to the absorption site.

4. No degradation or making up to the meking temperature of the drug. In other words, the polymer must be thermally stable under the heating to which it is subjected. This means, for example, that croselinked PVP, 20 which, in a controlled somosphere, does not present any detectable degradation up to 300°C, can be used for the treatment of drugs with high meiting temperatures; on the contrary, crosslinked dextran (caramelization temperature 120°C) can be used only with drugs with melting temperatures below 120°C; etc. The basic procedure of the heating technique of a mixture of an active drug and any (or combinations thereof) water-insoluble, swellable, hydrophylic polymer to which this invention relates, can be detailed as

A dry mixture of the drug and any of the swellable insoluble polymers eforemendoned (chosen among those with good thermal stability at the melting point of the drug) is placed in a container inside a thermoregulated high vecuum oven; after evacuation a nitrogen flow is established over the drug-polymer mixture and temperature raised to a value higher than the melting point of the drug. Alternatively the 30 mixture of the drug and the polymer is placed in the glass fissit of a rotating evaporator; after evacuation, a flow of nitrogen is established over the drug-polymer mixture and the glass flask placed in an oil bath of a temperature higher than the melting point of the drug. Any other heating apparatus (hot plats, muffle, tube oven etc.) can be usefully applied, as long as the temperature can be carefully checked and held constant. In any case the temperature must be raised to a value sufficient to ensure the melting of the drug.

The drug-polymer mixture is heated as long as the desired degree of amorphization of the drug is schleved, which can be checked by Differential Scanning Colorimetry. In fact the absence in the thermogram of the peak relative to the solid/liquid transition of the crystalline drug means the product is completely emorphous (enthalpy of meiting squal to zero). Obviously the heating process can be also stopped any time a degree (0-100%) of amorphization (measured by the reduction of the molting enthalpy) sufficient to 40 sensibly increase the discolution rate is achieved. Alternatively, the heating process can be stopped any time the original crystalline form of the drug has been transformed into another, more energetic form (this transformation is indicated by the shifting of the original endothermic pask to lower temperatures), leading to higher dissolution rate and bioavailability.

Weight ratios of drug and the polymer in the mixture to be heated can very from 1:0.1 to 1:100 w.w. drug: 45 polymer, preferably from 1:1 to 1:100 w.w. drug:polymer. For each drug: polymer weight ratio composition and each total amount of mixture, the time of heating necessary to achieve the desired degree of amorphization must be checked; therefore for each drug-polymer system the most practical combination of weight ratio and time of heating can be identified.

Examples of drug: polymer weight retio compositions, of heating temperature and time will be given later. The resulting heated mixture of the active drug and the available insoluble polymer can then be forced through a sleve to eliminate possible aggregates and subsequently mixed in any mixing device to warrant. further homogeneity. The resulting powdered heated system of the drug and the swelleble polymer can be subsequently used to prepare any desired docage form (e.g., capcules, tablets etc.) with or without the addition of any of the common excipients used in pharmaceutical formulations. Any ective drug with poor 68 dissolution characteristics can be treated by the ewellable polymer coheating technique described by this Invention. Non limiting examples of classes of drugs are: slightly soluble steroid hormones; non-steroidal hormones; andbiotics; antiinflammatory drugo; sadetivo drugo; etc. The amount of the polymer/drug system of the invention which is administered to a subject will depend upon a venery of factors including the drug employed, the condition to be treated and the age and condition of the patient.

60 The following non-limiting examples litustrate methods of making the preparations of the present invention.

Exemple 1

0.15 gram of crystalline methylhydroxyprogesterono ocetate (MAP) and 0.75 gram of crosslinted PVP were mbaed with a suitable mixing apparatus, subsequently placed in the glace fleak of a rotating eveporator and 65 heated in an oil bath at 216°C for 45 minutes, under nitrogen flow. The resulting MAP / crosslinked PVP

JUL 29 '99 11:44

3

10

GB 2 153 676 A

3

5

system was then sleved to 280 µm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solld dosage form.

Example 2

0.15 gram of crystalline indoprofen and 0.45 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 225°C for 30 minutes, under vecuum. The resulting indoprofen / crosslinked PVP system was then sleved to 260 µm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

10

Example 3

0.25 gram of crystalline indoprofen and 0.25 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 220°C for 30 minutes, under vacuum. The resulting indeprofen / crosslinked PVP system was then sleved to 280 µm 16 and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

15

Example 4

0.3 gram of crystalline grissofulvin and 0.9 gram of crosslinked PVP were mixed with a suitable mixing 20 apparetus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 235°C, for 20 minutes, under nitrogen flow. The resulting griseofulvin/crosslinked PVP system was then sieved to 260 μm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

25

20

25 Example 6

0.15 gram of crystalline griseofulvin and 0.45 gram of crossilnked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 235°C, for 45 minutes, under nitrogen flow. The resulting griseofulvin/crosslinked PVP system was then sieved to 260 µm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in 30 any desired solid dosage form.

30

Example 6

0.1 gram of crystalline griseofulvin and 0.5 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 235°C, 35 for 45 minutes, under vacuum. The resulting griseofulvin/crosslinked PVP system was then eleved to 260 µm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

40

35

Example 7

0.3 gram of crystalline indomethacin and 0.9 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 175°C, for 45 minutes under nitrogen flow. The resulting indomethacin/crosslinked PVP system was then sleved to 280 µm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in eny desired solid dosage form.

45

Example 8

45

0.1 gram of crystalline indomethacin and 0.5 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 175°C, for 45 minutes, under nitrogen flow. The resulting indomethacin/crosslinked PVP system was then sieved to 50 260 µm and mixed with a suitable mixing apparatus. This powdered system could than be incorporated in any desired solid dosage form.

FO

Example 9

0.3 gram of crysteiline indomethacin and 0.9 gram of crosslinked sodium carboxymethylcallulose were 55 mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 175°C, for 45 minutes, under nitrogen flow. The resulting indomethacin/crosslinked sodium carboxymethylcellulose system was then sleved to 260 µm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

56

80 Differential scanning calorimetry data

The D.S.C. (TA 3000, Mettler) data relative to the preparation by heating containing MAP described in example 1, are presented in Table 1 : after 45 minutes of heating at 216°C the mixture MAP : crosslinked PVP 1:5 w/w presents a complete amorphization (no residual crystallinity) of MAP.

60

As shown in Table 2, both with a mixture 1:1 w/w indoprofen : PVP crosslinked and a mixture 1:3 w/w, 65. after 30 minutes at 225°C or at 220°C a complete amorphization is achieved.

In the case of the griceofulvin heated systems, as shown in Table 3, the heating for 20 minutes at 235°C of a 1:3 w/w grissofulvin: crosslinted PVP mixture leads to a ~80% reduction of the original heat of fusion and to a parallel shifting of the melting point to a lower value. A complete amorphization is achieved, both for the 1:3 and 1:5 w/kv mbatures, after 45 minutes of heading at 235°C.

As shown in Table 4, mixtures of Indometherin and crosslinked PVP, both at 1:3 and 1:5 weight rotice, after heating at 175°C for 45 minutes, present a ~80% reduction of the original heat of fucion, whereas the mixture with crosslinked codium carboxymethylcallulose, at 1:5 w/w ratio, at the cerns time of heating, loads about a complete emorphizetion.

10 Solubility dem

A) MAP/swellable polymer heated mixture

The solubility of the MAP/swelleble polymer hasted mixture described in Example 1 was assessed by placing on excess amount of the powder, equivalent to 50 mg of MAP, in fleets containing 60 ml of pH 5.5 15 buffer solution, at 37°C; the flesix were placed in a chaking thermoduted apparatus and aliquote of cample solution were taken by filtering through a Millipore membrane; concentration of MAP in the filtered allquot was determined both by spectrophotometry (SP8-100 Pye Unicem), at $\lambda = 247$ nm, after dilution with methanol, and by HPLC (column: Spherisorb S30 D52, Phase Sep.; mobile phase: occanitrile/exciter 70/30 v/v; flow rate : 1 ml/min; U.V. detection; $\lambda = 242$ nm), after dilution with acatenitrile.

The solubility date of the MAP/crosslinked FVP 1:5 w/w heated mixture described in Example 1 are reported in Table 5. It is possible to observe that the heated mixture prepared by the rechnique described by this invention originates MAP concentrations higher than the pure MAP or the physical mixture of MAP and crosslinted PVP. Even more important is to observe that the heated mixture proves to have a better solubility percorn than the MAP/crosolinked PVP 1:5 w/w system propered by the colvent swelling technique (4 ml of 26 50.0 mg/ml methylenechloride solution of WAP over 1 g of crosslinked PVP).

B) Indoprofen/ewaliable polymer hosted mixtures

The colubility of the indeprefen/crosslinked PVP heated mixtured described in Exemples 2 and 3 was measured by following the procedure used for the MAP dystems and a pH 2.0 buffer solution; the indeproten 30 concentrations were determined by spectrophotometry ($\lambda = 280$ nm).

As shown in Table 8, both the indeprefer/crosolinited PVP 1:1 and 1:3 w/w heated mixtures originate Indeprefen concentrations higher than in the case of the pure drug and of the physical mixture of the drug and the crosslinked PVP. Furthermore the heated mixtures originate indeprefer concentrations so high ല the indeprefer/crosslinked PVP 1:4 w/w system prepared by the solvent awelling method (2.5 mi of 100 39 mg/ml dimethylformamide solution of indeprofen over 1 g of crosellniced PVP), but it is important to stress that these concentrations are obtained at drug : polymer ratios (1:1 and 1:3 w/w) lower than the most favourable ratio which could be obtained by the solvent awelling method (1:4 w/w).

C) Griccolutvin/swellable polymer heated mixtures

The colubility of the Gricefulvin/crosslinited PVP heated mbriums described in Exemples 4, 5 and 6 woo measured by the following the procedure used for the MAP systems and a pH 7.5 buffer solution; the Grissfulvin concentrations were determined by exectrophotometry (A= 284 nm).

As shown in Table 7, the Griscofulvin/crosolinited PVP hosted mixtures originate drug concentrations very much higher than the pure Griscofulvin or the physical mixture of Griscofulvin and crosslinited PVP. 46 Furthermore, also the drug concentrations originated by the system prepared by the colvent swelling technique (& mi of 83.3 mg/mi dimethylformamide solution of Grissofulvin over 1 gram of crosslinked PVP) are very much lower than the concentrations originated by the heated mixtures.

D) Indomethocin/owellable polymer heated mixtures

The solubility of the Indomethic in/cresslinked PVP heated mixtures described in Exemples 7, 8 and 9 was measured by following the procedure used for the MAP systems and a pH 6.8 buffer colution; the Indomethad concentrations were determined by spectrophotometry ($\lambda = 317$ nm).

As chown in Table 8, the indomeshadin concentrations originated at chorar times by the heated mixtures, both containing crosslinted PVP and crosslinted Sadium Corbosymothylcelluloce, are higher than the 55 concentrations given by the pure drug and the physical mixture drug/crosslinked PVP. Furthermore, Indomethed n concentrations originated by the heated mbraures are so high as those obtained by the colvent swelling technique (4 ml of 50.0 mg/ml acestone colution of indomethecin over 1 gram of creatilitied PVP). but these concentrations are also obtained at drug : polymer rades (1:3) lower than the most favourable ratio which could be obtained by the solvent swelling method (1:5 $ext{wh}$).

On the basis of the previously shown solubility data, it is possible to conclude that the drug/twellable water insoluble polymer systems prepared by the heading technique described by this invention possess the property to increase the colubilization characterizties of the drugs. In fact solubility values not only higher than those obtained by the corresponding polymer/drug physical mbaures can be exhibited but also higher than those originated by drug/swellable water-incoluble polymer systems prepared by the colvent swelling technique. Anyway, it was evidentiated that also when the systems prepared by the heating technique

JUL 29 '99 11:45 7034124866 PAGE.08

19

10

20

23

35

30

40

45

€0

മാ

6

5

originated drug solubility data as high as the concentrations obtained by the solvent swelling systems, these concentrations were achieved at more favourable drug : polymer ratio, i.e. using less polymer.

		TABLE 1			_
5 Diffe Hea	erential Scanning Calorimetry Date of M ted Mixture.	ethylhydroxyprog	pesterane a	cetate (MAP) /Swellable Pol	ymer Ymer
0	System	Melting Point °C	Heat of Fusion Jig	% Residual of Original Heat of Fusion	10
	Pure crystalline MAP	205-208	0.88	100	
5	MAP/crosslinked PVP 1:5w/w (heating method, 45 mln et 216°C) Example 1	• •	•	0	15
0		TABLE 2			20
Diff	ferential Scanning Calorimetry Data of Ir	ndoprofen/Swellal	bia Polymei	r Heated Mixtures.	
:5	System	Melting Point °C	Heat of Fusion Jig	% Residual of Original Heat of Fusion	25
	Pure crystalline indoprofen	212-215	134.6	100.00	
0	Indoprofen/crosslinked PVP 1:1w/w (heating method 30 min at 220°C) Example 3	-	0	0	30
5	Indoprofen/crosslinked PVP 1:3w/w (heating method 30 min at 225°C) Example 2	-	0	0 .	36
10		TABLE 3			40
Dif	ferential Scanning Calorimetry Data of C	Griseofulvin/Swell	lable Polym	er Heated Mixtures.	
1 5	System	. Melting Polnt °C	Heat of Fusion Jig	% Residual of Original Heat of Fusion	46
	Pure crystalline Griseo-	218.8	119.2	100	
	fulvin				50

45	System	Melting Point °C	Heat of Fusion Jig	% Residual of Original Heat of Fusion	46
	Pure crystalline Griseo- fulvin	218.8	119.2	100	50
	Griseofulvin/crosslinked PVP 1:3w/w (heating method, 20 min et 235°C) Example 4	202.7	10.4	8.7	56
56	Griseofulvin/crosslinked PVP 1:3w/w (heating method, 45 min at 235°C) Example 5	-	0	0	60
60 /	Griseofulvin/crosslinked PVP 1:5w/w (heating method, 45 min at 235°C) Example 6	•	0	0	63
65 '					65

T	۸	P.	A

Differential Scanning Calorimetry Deta of Indomethacin/Swellable Polymer Heated Mixtures.

5	System	Melting Point °C	Heat of Fusion Jig	% Residual of Original Heat of Fusion	6
10	Pure crystalline indome- thacin	160.2	110.8	100	10
15	Indomethacin/crosslinked PVP 1:3w/w (heating method, 45 min at 176°C) Example 7	160.2	9.7	8.6	15
20	Indomethecin/crossiinked PVP 1:5w/w (heating method, 45 min at 175°C) Example 8	160.8	11.3	10.9	20
25	Indomethacin/crosslinked Sodium Carboxymethylcallu- lose 1:3w/w (heating method, 45 min at 175°C) Example 9	•	0	0	25

TABLE 5

30	Solubility Data (mcg/ml) of Methylhydorxyprogesterone acetate (MAP)/Swellable Polymer Heated Mixture	30
	(nH 5.5 phosphate buffer, 37°C)	

	_	Time				
35	System	5 mln	15 min	1 hr	6 hrs	35
	Pure crystalline MAP	<0.04	0.32	0.68	1.00	
40	Physical Mixture 1:3 w/w MAP/crosslinked PVP	0.85	1.18	1.34	1,21	40
45	MAP/crosslinked PVP 1:5w/w (heating method, 45 min at 216°C) Example 1	3.83	6.10	4,78	3.28	45
40	MAP/crosslinksd PVP 1:5w/w (solvent swelling method)	1.00	1.61	1.69	2.04	

7 GB 2 153 676 A 7 TABLE 6 Solubility Data (mcg/ml) of Indoprofen/Swellable Polymer Heated Mixtures (pH 1.2 buffer solution, 37°C) Time 5 System 24 hrs 15 min 1 hr 3 hrs 5 min 10.3 3.0 4.8 1.6 Pure crystalline indopro-10 fen 10 11.3 10.2 9.6 8.3 8.2 Physical Mixture 1:3 w/w Indoprofen/crosslinked PVP 15 19.2 19.1 19.1 13.9 Indoprofen/crosslinked PVP 15 1:3 w/w (heating method, 30 min et 225°C) Example 2 20 14.0 17.0 17.0 12.9 Indoprofen/crosslinked PVP 20 1:1 w/w (heating method, 30 min at 220°C) Example 3 25 14.8 15.7 16.8 Indoprofen/crosslinked PVP 19.3 25 1:4 ww (solvent swelling method) TABLE 7 30 Solubility Data (mcg/ml) of Griseofulvin/Swellable Polymer Heated Mixtures (pH 7.4 buffer solution, 37°C) 30 Time System 35 24 hrs 6 min 16 min 1 hr 3 hrs 35 10.9 11.3 14.9 11.0 9.1 Pure crystalline Griseofulvin 19.3 21.2 23.9 18.9 Physical Mixture 1:3 w/w 40 Griseofulvin/crosslinked PVP 60.9 62.8 66.5 65.5 64.8 Griseofulvin/crosslinked PVP 1:3w/w (heating method 45 20 min at 235°C) Example 4 -96.3 98.7 96.2 100.6 8B.5 Griseofutvin/crosslinked 60 PVP 1:3 w/w (heating method 50 45 min et 235°C) Example 5 80.6 81.2 107.1 87.5 Grissofutvin/crosslinked 55 PVP 1:5 w/w (heating method 55 45 mln at 235°C)

JUL 29 '99 11:46 7034124866 PAGE.11

19.1

60

19.9

24.2

24.7

24.0

Example 6

ling method)

60

Griseofulvin/crosslinked

PVP 1:3 w/w (solvent swel-

JU1-29-99 11:42AM;

GB 2 153 678 A

8

TABLE 8

Solubility Data (mcg/mi) of Indomethacin/Swellable Polymer Heated Mixtures (pH 6.8 buffer solution, 37°C)

5			Time					5
	System	5 min	16 mln	1 hr	3 hrs	24 hrs		
10	Pure crystalline Indomethacin	230.2	358.2	482.1	502.8	502.0		10
	Physical Mbdure Indomethach/crosslinked PVP 1:5 w/w	184.7	254.3	364.3	389.6	522.5		
15	Indomethacin/crosslinked PVP 1:5 w/w (heating method 45 min at 175°C) Example 8	489.1	515.4	499.0	602.5	•		15
20	Indomethacin/crosslinked PVP 1:3 w/w (heating method 45 min at 175°C) Example 7	473.1	484.1	485.3	483.1	•		20
25	Indomethacin/crossfinited Sodium Carboxymathylcallu- lose 1:3 w/w (heating method, 45 min at 175°C)	418.8	473.4	481.5	480.1	484.3		25
30	Example 9 Indomethacin/crossitnked PVP 1:5 w/w (solvent swell- ing method)	464.6	475.5	475.4	489.6	496.0		
35 C	LAIMS							35

A process for loading a water-swellable water-insoluble polymer with a biologically active substance or substance which is converted thereinto in vivo, which process comprises (i) prepering a mixture of a said substance with a water-swellable water-insoluble polymer which is stable under the heating to which the mixture is subjected in step (ii) in a weight ratio of the said substance:polymer of from 1:0.1 to 1:100 and (iii) heating said mixture up to the melting temperature of the said substance.

2. A process according to claim 1 in which the said substance is a drug or pro-drug.

3. A process according to claim 1 or 2 in which said polymer is cross-linked polyvinylpyrrolidone or accoss-linked sodium carboxymethylcalluloss.

 A process according to any one of the preceding claims in which two or more water-swellable, water-insclubis polymers are employed in step (I).

5. A water-swellable; water-insoluble polymer which has been loaded with a biologically active substance or substance which is converted thereinto in vivo in a weight ratio of the said substance: polymer 50 of from 1:0.1 to 1:100 by a process as claimed in any one of the preceding claims.

6. A pharmaceutical composition comprising a water-evellable, water-insoluble polymer loaded with a biologically active substance or substance which is converted thereinto in vivo which has been prepared by a

process as dalmed in any one of claims 1 to 4 or which is as claimed in claim 5.

7. A composition according to claim 6 further comprising a pharmaceutically acceptable exciplent.

8. A process for loading a water-swellable, water-insoluble polymer with a biologically active substance or substance which is converted thereinto in vivo, said process being substantially as hereinbefore described in any one of Examples 1 to 9.

9. A water-swellable, water-insoluble polymer loaded with a biologically active substance or substance which is converted thereinto in vivo, said loaded polymer being substantially as hereinbefore described in 80 any one of Examples 1 to 9.

Princed in the UK for HMSCO, 09312995, 769, 7190, 7190, Published by The Peters Office, 25 Southempton Buildings, London, WCIA 1AY, from which applies may be obtained.

45

50